REMARKS

Claims 12-21, 24-39, 43-47 and 50-59 are pending in the application. Claims 12-21, 24-29, 40 and 43-45 have been withdrawn from further consideration. Claims 30-39, 46-47, and 50-59 have been examined on the merits. Amendments to claims 30 and 52 are made to remove the unnecessary word "unhybridized" from the claims because the recited phrase "comprising single-stranded" within the context of the invention does not read on double-stranded nucleic acid. The amendments to claims 46 and 47 are made to correct typographical errors. Thus, no new matter has been inserted into the application.

Double Patenting

Claim 42 has been provisionally objected to under 37 CFR 1.75 because claim 42 is considered to be substantially duplicative of claims 33 and 39. Applicants traverse this objection. Reconsideration and withdrawal thereof are respectfully requested.

Claim 42 has been canceled. Therefore, this objection has been overcome.

Rejection Under 35 U.S.C. § 112, Second Paragraph

Claims 41 and 42 have been rejected under 35 U.S.C. § 112, Second Paragraph, as being indefinite for lacking antecedent basis for various recited language. Applicants traverse this rejection. Reconsideration and withdrawal thereof are respectfully requested.

Claims 41 and 42 have been canceled. Accordingly, this rejection has been overcome.

Rejection Under 35 U.S.C. § 103(a) Over Hellmann (Virology. Vol. 143, pp. 295-303 (1985)) in view of Moon (J. Biol. Chem. 275(18), pp. 4647-4653 (2000)) and LaPlante (Biochem J. Vol. 348, pp. 189-199 (2000))

The Examiner has maintained the rejection of claims 38, 46 and 47 as being obvious over Hellmann in view of Moon and LaPlante. Applicants traverse this rejection. Reconsideration and withdrawal thereof are respectfully requested.

In the Office action of October 15, 2004, the Examiner appears to indicate that the substance of the instant rejection is substantially the same as set forth in a new rejection under 35 U.S.C. §103(a) that is based on art cited in the instant rejection, and encompasses both the instantly rejected claims and other claims. In view of this comment by the Examiner, rather than responding to the substance of the rejection at this point, Applicants provide comments in response to the new rejection under 35 U.S.C. §103(a) set forth below.

Rejection Under 35 U.S.C. § 103(a) Over Hellmann in view of Moon, LaPlante, Hu '062 (U.S. Patent No. 6,107,062), and Gewirtz (Proc. Natl. Acad. Sci. 1996. v. 93, pp. 3161-3163)

Claims 22, 23, 30-39, 41, 42, and 46-61 have been rejected as being obvious over Hellmann in view of Moon, LaPlante, Hu '062 and Gewirtz. Applicants traverse this rejection. Reconsideration and withdrawal thereof are respectfully requested.

Hellmann

Hellmann discloses an M13 molecule with a Tobacco Vein Mottling Virus (TVMV) insert sequence. Hellmann further discloses performing DNA:RNA hydridization assays with the M13 molecule in a reticulocyte lysate cell-free translation system, the so called hybrid-arrested translation system.

Hellmann fails to disclose or suggest mixing the M13 molecule with a transfection effective composition containing lipids such as cationic lipids or liposomes because Hellmann's assays with the M13 molecule is conducted entirely in a cell-free system, and there is no disclosure or suggestion found in Hellmann to combine the M13 molecule with any cell transfection reagent for introducing the M13 molecule into a eukaryotic cell.

Moon

Moon discloses a ribbon-type antisense oligonucleotide. However, Moon fails to disclose or suggest the presently claimed inventive composition, which is directed to a large circular single-stranded nucleic acid molecule, which is at least about 3,000 nucleotides long and/or comprises a recombinant bacteriophage or phagemid genome.

LaPlante

LaPlante discloses an antisense cDNA for the gene encoding CHERP. However, LaPlante fails to disclose or suggest the presently claimed inventive composition, which includes a large circular single-stranded nucleic acid molecule, which is at least about 3,000 nucleotides long and/or comprises a recombinant bacteriophage or phagemid genome.

Hu '062

Hu '062 is relied on for the disclosure of a plasmid that expresses several target specific antisense RNA, which inhibits the target gene expression. Hu '062's research focus uses a cell-based system in which the cells are transfected with a double-stranded plasmid. Hu '062 is mainly concerned with optimizing expression of its antisense RNA producing method and its effectiveness within a cell. Hu '062 is not concerned at all with any cell-free system. Hu '062 is not concerned with any translational mapping that would warrant turning to a reference like Hellmann for guidance. To Hu '062, the Hellmann reference would be outside the purview of its

research and therefore, Hu '062 would not have considered the Hellmann reference to be of any help in Hu '062's cell based target gene expression inhibition methods.

Gewirtz

Gewirtz discloses that lipid transfection agents may be used with oligodeoxynucleotides and plasmid DNA.

Distinctions of the present invention over the cited references

Basic considerations which apply to obviousness rejections

When applying 35 U.S.C. 103, the following tenets of patent law must be adhered to:

(A) The claimed invention must be considered as a whole;

(B) The references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination;

(C) The references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention; and

(D) Reasonable expectation of success is the standard with which obviousness is determined. *Hodosh v. Block Drug Co., Inc.*, 786 F.2d 1136, 1143 n.5, 229 USPQ 182, 187 n.5 (Fed. Cir. 1986). (MPEP 2141).

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable

expectation of success must both be found in the prior art, and not based on applicant"s disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

The initial burden is on the examiner to provide some suggestion of the desirability of doing what the inventor has done. "To support the conclusion that the claimed invention is directed to obvious subject matter, either the references must expressly or impliedly suggest the claimed invention or the examiner must present a convincing line of reasoning as to why the artisan would have found the claimed invention to have been obvious in light of the teachings of the references." *Ex parte Clapp*, 227 USPQ 972, 973 (Bd. Pat. App. & Inter. 1985). MPEP 2142.

Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either explicitly or implicitly in the references themselves or in the knowledge generally available to one of ordinary skill in the art. "The test for an implicit showing is what the combined teachings, knowledge of one of ordinary skill in the art, and the nature of the problem to be solved as a whole would have suggested to those of ordinary skill in the art." *In re Kotzab,* 217 F.3d 1365, 1370, 55 USPQ2d 1313, 1317 (Fed. Cir. 2000). See also *In re Lee,* 277 F.3d 1338, 1342-44, 61 USPQ2d 1430, 1433-34 (Fed. Cir. 2002) (discussing the importance of relying on objective evidence and making specific factual findings with respect to the motivation to combine references); *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). MPEP 2143.

In order to establish *prima facie* obviousness of the invention over the cited references, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify or combine reference teachings. The Federal Circuit has produced a number of decisions overturning obviousness

rejections due to a lack of suggestion in the prior art of the desirability of combining references, as discussed in the aforementioned section. In the present situation, the Examiner has failed to establish *prima facie* obviousness of the present invention over Hellmann, Moon, LaPlante, Hu '062 and Gewirtz.

Hellmann's disclosure and the problem to be solved.

Hellmann discloses an M13 construct with a Tobacco Vein Mottling Virus insert sequence, which is used to create DNA:RNA hybrid as used in an *in vitro* cell-free hybrid arrest assay. Hellmann is focused on developing an assay system to determine the origin of the polypeptide product encoded by the 5'- terminal region of the RNA of the potyvirus. Hellmann is further focused on precisely mapping the potyviral proteins and understanding the translational mechanisms by which they are produced. Hellmann states that single-stranded DNAs derived from plasmids containing approximately 95% of the sequences of TVMV RNA arrest the translation of specific portions of TVMV RNA and discovered that synthesis of P75 is initiated near the 5' terminus (paragraph bridging pages 23-24). To solve the problem of understanding the translational mechanisms of potyvirus, Hellmann chose to employ a cell-free translation system using single-stranded DNA fragments obtained from M13, which contains the TVMV inserts because "initial attempts to perform hybrid-arrested translation experiments using double-stranded recombinant plasmids were unsuccessful due to rapid annealing of the DNA strands under the hybridization conditions use." (Page 25, paragraph bridging left and right columns).

Hellmann's research focus is on using a single-stranded DNA in cell-free hybrid arrested translation experiments because Hellmann is interested in the problem of solving the translational machinery of potyvirus for which the cell-free system is a more helpful

experimental methodology than cell-based methodology. Accordingly, Hellmann fails to disclose or suggest transfecting any eukaryotic cell. Further, Hellmann fails to disclose or suggest transfecting any cell with a single-stranded DNA. Therefore, the reach and limit of the disclosure of the Hellmann reference is the cell-free system.

Hellmann is not combinable with Moon, LaPlante, Hu '062, or Gewirtz

Applicants submit that the Hellmann reference and the Moon reference fail to be combinable with each other. The Moon reference discloses a composition that includes a 116-mer stem-loop DNA structure and a transfection effective carrier. Since Hellmann discloses only a cell-free system, with its own set of experimental challenges, there would be no reason for a person of ordinary skill in the art reviewing the Hellmann reference to consult the Moon reference directed to gene expression within a cell. Cell-free (Hellmann) and cell-based (Moon) systems each present separate, unique challenges. A person of skill in the art contemplating carrying out a cell-free based expression studies according to Hellmann would not look to a cell-based gene expression system such as disclosed in Moon for guidance. Therefore, the Hellmann and Moon references are not analogous art and are not combinable.

Moreover, Moon states at page 4652, penultimate paragraph as follows:

> We used cationic liposomes to enhance the cellular uptake of RiAS oligos. From the experience of our own and other groups, a meaningful level of AS oligo uptake should be consistently obtainable when carried into cells by liposomes, regardless of the size of AS oligos (31, 32). Therefore, the relatively large size or RiAS oligos should not pose a problem for efficient cellular uptake. (emphasis added)

Moon suggests that the 116-mer oligonucleotide (RiAS) is relatively large, and that even this large an oligonucleotide should be able to be transfected into the cell. Moon considers 116-

mer to be large. And yet makes no mention of the desirability or capability of transfecting a large circular single-stranded nucleic acid that is at least 3,000 bases long into a mammalian cell. Thus, it cannot be fairly said that the 116-mer transfection attained in Moon alone is suggestive of transfection effectiveness or desirability of a large circular single-stranded nucleic acid that is at least 3,000 bases long. Oligonucleotides, double stranded nucleic acids, linear nucleic acids, large circular single-stranded nucleic acids and so on are each biochemically, conformationally and sterically unique. There is a level of unpredictability as to how they would behave and whether they would be useful inside of a cell. Therefore, since Moon does not disclose or suggest transfection appropriate to the large circular single-stranded nucleic acid of the claimed invention, Moon fails to be applicable to the presently claimed invention.

LaPlante's disclosure of a human CHERP gene cDNA cloned into a plasmid and producing mRNA does not provide any motivation to transfect a large circular single-stranded nucleic acid molecule into a mammalian cell as in the claimed invention. LaPlante essentially discloses two types of nucleic acids – plasmid DNA and linear RNA. since LaPlante does not disclose or suggest transfection appropriate to the large circular single-stranded nucleic acid of the claimed invention, LaPlante fails to be applicable to the presently claimed invention. Furthermore, Hellmann and LaPlante are again not combinable as references because they are in non-analogous art of cell-free and cell-based assay systems.

Applicants submit that the Hellmann reference and the Hu '062 patent fail to be combinable with each other. Hu '062 is firmly focused on inhibiting target gene expression by the expression of exogenously introduced plasmid DNA that expresses antisense RNA. Hu '062's research field is limited to the realm of transfecting cells, assaying for gene expression within a cell background, and assaying for changes in cell morphology. The methods and

techniques employed richly revolve around cell cultures and assays using live organisms, which extend to therapeutics and treatment of disease, specifically AIDS. This is in stark contrast to the Hellmann reference, which is directed to a cell-free assay system that employs a single-stranded M13 phage construct to determine the translational mechanism of the potyvirus. Hellmann fails to disclose any information regarding any cell-based type of system. And a person in the art of target gene inhibition by expression of antisense RNA would not look to a cell-free assay system for guidance in solving its problems.

Since the purposes for which each reference uses either the single-stranded or double-stranded form of either the phage or the plasmid vector are divergent, a person of ordinary skill in the art reviewing the Hellmann reference would not be motivated to consider using a plasmid DNA expressing antisense RNA to assist in solving the hybridization problem discussed in the Hellmann reference. And *vice versa*, a person in the cell-based antisense therapy field would not be motivated to consider using a single-stranded M13 vector construct of Hellmann in solving its therapeutic focus, as there is simply no motivation found in either reference to combine these references.

The Gewirtz reference discloses transfecting oligonucleotides and double stranded plasmid DNA into mammalian cells by complexing these types of nucleic acids with a transfection effective carrier. Gewirtz is concerned with better efficiency of oligonucleotides because this was the major focus of antisense research at the time. Transfection effective agents for nucleic acids were known in the art at the time of the invention as exemplified by Gewirtz. It is noted however that Gewirtz makes no mention expressly or impliedly that a large circular single-stranded nucleic acid as in the claimed invention may be transfected into eucaryotic cells. Furthermore, again as with the other cited references, the Gewirtz reference discloses a cell-

based transfection oriented technology, which is not analogous to the cell-free system that Hellmann discloses. Therefore, these references fail to be combinable with each other.

Hindsight reconstruction

Applicants submit that the Examiner has cobbled together the cited five (5) references in an attempt to show obviousness of the claimed composition. The Examiner has cited these references with hindsight vision afforded by the claimed invention. Clearly, in order to establish obviousness of the claimed composition, it is not enough to show that each of the separate ingredients are in existence, as the Examiner has done. The Examiner must provide references that show the desirability and the motivation for combining the references to arrive at the claimed composition. All of the cited references fall short of this simply because none of the cited references recognizes or appreciates that the effective usefulness of transfecting these large circular single-stranded nucleic acid molecules into eucaryotic cells.

Indeed, Hellmann shows the opposite of the inventive concept because Hellmann shows a large circular single stranded nucleic acid molecule that is used in a cell-free system. Therefore, Hellmann certainly fails to providc any motivation to insert its nucleic acid into a eukaryotic cell, and further, Hellmann is not applicable to the cell-based transfection system of the claimed invention.

It must be appreciated that Applicants have at the time of the invention demonstrated for the first time that transfecting these large circular single-stranded nucleic acids into eukaryotic cells resulted in useful and effective antisense effects, which was not recognized before in the art because the art at the time was focused on injecting small oligonucleotides. No one had

appreciated that a large circular single-stranded nucleic acid such as instantly claimed could be used in to effect an antisense response.

CONCLUSION

None of the cited references points to any desirability or motivation to make the claimed large circular single-stranded nucleic acid composition because none of the references discloses or suggests the desirability of transfecting a large circular single-stranded nucleic acid molecule into eucaryotic cells. Accordingly, the presently claimed invention is not obvious over the cited references.

It is believed that the application is now in condition for allowance. Applicants request the Examiner to issue a notice of Allowance in due course. The Examiner is encouraged to contact the undersigned to further the prosecution of the present invention.

The Commissioner is authorized to charge JHK Law's Deposit Account No. **502486** for any fees required under 37 CFR §§ 1.16 and 1.17 that are not covered, in whole or in part, by a credit card payment enclosed herewith and to credit any overpayment to said Deposit Account No. **502486**.

Respectfully submitted,

JHK Law

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